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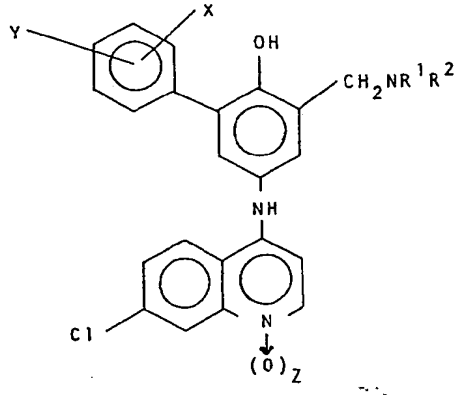
(54) Substituted-5-((7-chloro-4-quinolinyl)amino)-3-(amino-methyl)-(1,1'-biphenyl)-2-ol compounds; processes for their production; pharmaceutical compositions containing the compounds; intermediate compounds for use in said processes; and production of the intermediates.

(57) Substituted-5-[(7-chloro-4-quinolinyl)amino]-3-(aminomethyl)-[(1,1'-biphenyl]-2-ol compounds and salts thereof; and processes for their production are disclosed. In addition, antimalarial pharmaceutical compositions including such compounds and methods of treatment employing the compositions are taught. Also disclosed are intermediates for use in producing the substituted compounds. The substituted compounds are those of the formula:-



wherein X is a hydrogen, fluorine, bromine or chlorine atom or a lower alkyl radical; Y is a chlorine, fluorine or bromine atom or a trifluoromethyl, lower alkoxy, cyano, hydroxy, nitro, lower alkylthio, amino, lower alkyl amino, di(lower alkyl) amino, pyrrolidino or piperidino radical; R^1 and R^2, which are the same or different, are each a hydrogen atom or a lower alkyl radical, or R^1R^2N taken together is a pyrrolidino, piperidino or homopiperidino radical of which the heterocyclic ring is unsubstituted or substituted by from one to four lower alkyl radicals; Z is zero or one.

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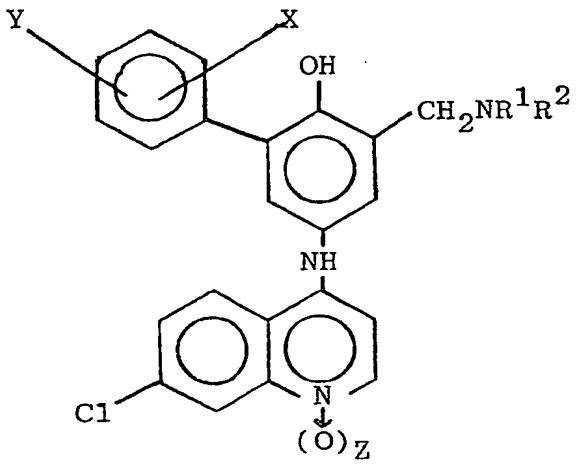
SUBSTITUTED-5-[(7-CHLORO-4-QUINOLINYL)AMINO]-3-(AMINOMETHYL)-[1,1'-BIPHENYL]-2-OL COMPOUNDS; PROCESSES FOR THEIR PRODUCTION; PHARMACEUTICAL COMPOSITIONS CONTAINING THE COMPOUDS; INTERMEDIATE COMPOUNDS FOR USE IN SAID PROCESSES; AND PRODUCTION OF THE INTERMEDIATES.

This invention relates to substituted-5-[(7-chloro-4-quinolinyl)amino]-3-(aminomethyl)-[1,1'-biphenyl]-2-ol compounds and salts thereof; to processes for their production; to intermediate compounds for use in the processes; and to antimalarial pharmaceutical compositions incorporating the substituted compounds.

More particularly one aspect of the present invention relates to compounds of the following general formula:



or a pharmaceutically acceptable salt thereof; wherein X is a hydrogen, fluorine, bromine or chlorine atom or a lower alkyl radical; Y is a chlorine, fluorine or bromine atom or a trifluoromethyl, lower alkoxy, cyano, hydroxy, nitro, lower alkylthio, amino, lower alkyl amino, di(lower alkyl) amino, pyrrolidino or piperidino radical; R^1 and R^2, which are the same or different, are each a hydrogen atom or a lower alkyl radical, or R^1R^2N taken together is a pyrrolidino, piperidino or homopiperidino radical of which the heterocyclic ring is unsubstituted or substituted by from one to four lower alkyl radicals; Z is zero or one; a lower alkyl radical is an alkyl radical containing from one to six carbon atoms; and a lower alkyoxy radical is an alkyoxy radical containing from one to six carbon atoms.

Preferably X is a hydrogen or chloro and Y is chloro or fluoro. Also, preferably X is in the 3-position and Y is in the

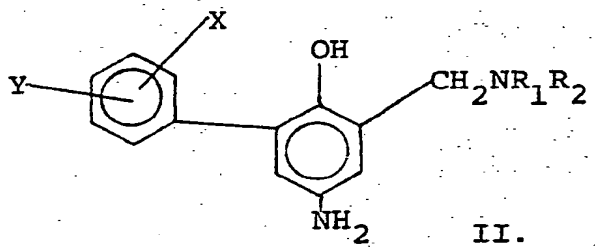
two or four position, R_1 is lower alkyl, R_2 is hydrogen or lower alkyl and Z is zero or one.

The term "lower alkyl" is intended to mean a hydrocarbon fragment of from one to six carbon atoms.

The term "lower alkoxy" is intended to mean a lower alkyl group linked directly to an oxygen atom by a single bond.

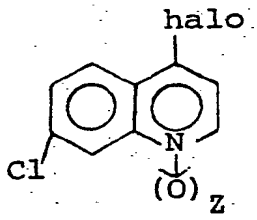
The term "pharmaceutically acceptable salts" is intended to mean the relatively non-toxic acid-addition salts, such as the hydrochloride sulfate, phosphate, acetate, benzoate methane sulfonate, salt or the salt formed with a base, such as the sodium, potassium or ammonium salt. In addition, of special interest are typical repository salts, such as the pamoate.

The compounds of the invention can be prepared by coupling a compound of the formula



II.

with a compound of the formula



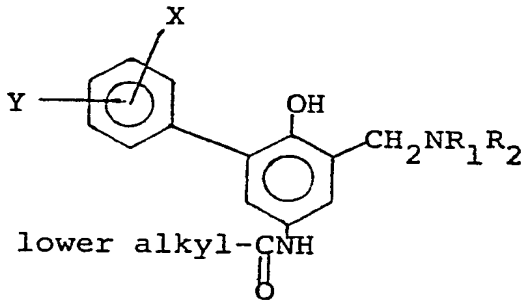
III.

wherein R_1, R_2, X, Y and Z are as previously defined and halo is iodo, chloro or bromo.

Approximately equimolar quantities of reactants are employed in a polar solvent, such as ethanol, dimethylformamide, dimethylsulfoxide, acetonitrile, etc., or mixture thereof. The reaction requires the presence of an acid, such as hydrochloric, benzenesulfonic, etc., in at least catalytic amounts to quantities on a molar basis in excess of the reactants.

The reaction is carried out for periods of about one-half hour to twelve hours, preferably one to five hours, at a temperature range of about 10°C to 150°C, preferably 35°C to 80°C.

While the starting material of the formula III is known, compounds of the formula II are prepared by removing an acyl group from a compound of the formula

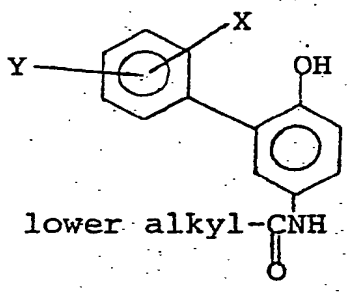


IV.

where X, Y, R_1 and R_2 are as previously defined.

The term "homopiperidino" is used herein to mean a homologue of a piperidino radical having an extra methylene group in the ring, that is a seven membered ring containing one nitrogen and six carbon atoms.

The intermediates of the formula IV are prepared by reacting a compound of the formula



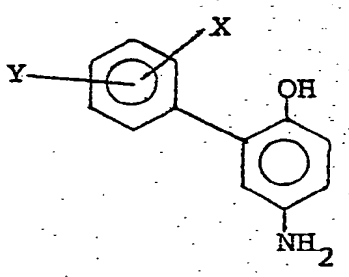
V.

with formaldehyde and an amine of the formula

$$HNR_1R_2 \cdot HCl$$

where X, Y, R_1 and R_2 are as previously defined.

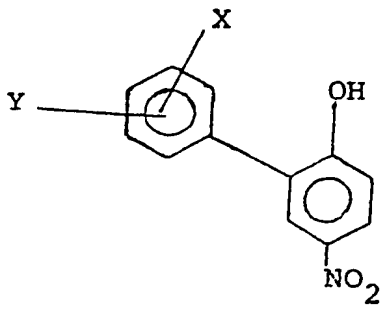
The intermediates of the formula V are prepared by acylating a compound of the formula



VI

using a lower alkyl acyl halide or anhydride.

The intermediates of the formula VI may be prepared by two routes, the much preferred procedure, which is a part of this invention, utilizes the reduction of a compound of the formula

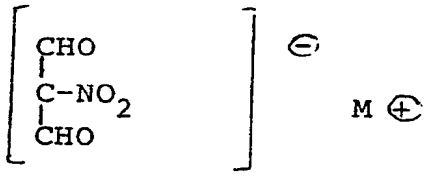


VII

wherein X and Y are as previously defined.

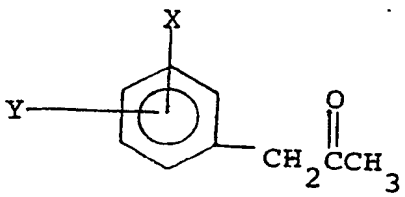
The reduction can preferably be carried out catalytically using finely divided Ni, Pd, Pt, etc., which may or may not be on a support such as carbon, alumina, etc., and hydrogen in a polar solvent, such as ethanol, acetic acid, etc. The reaction requires from only about a few minutes to about six hours at from 10°C to 60°C.

The intermediates of the formula VII are obtained by reacting a compound of the formula



VIII

wherein $M^{\oplus}$ is a cation, preferably sodium or potassium, with a compound of the formula



IX

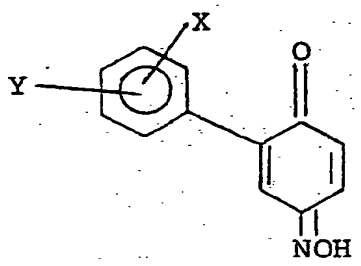
wherein X and Y are as previously defined, especially when X is hydrogen and Y is in the para position.

Approximately equimolar quantities of reactants are employed in a polar solvent, such as water, ethanol, dimethylformamide, dimethylsulfoxide, etc., or mixture thereof. The reaction requires the presence of a base such as sodium hydroxide, potassium hydroxide, etc., in at least an equimolar ratio when compared to reactants, preferably on a two to one basis in favor of the base.

The reaction is carried out for periods of from two to twenty-four hours at a temperature range of 10°C to 80°C, preferably 15°C to 40°C.

The compounds of formula IX are known or easily prepared according to methods in the literature.

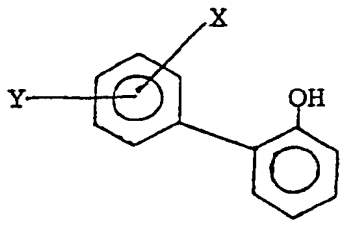
The second route that may be used to prepare compounds of the formula VI involves reacting a compound of the formula



X

with sodium dithionate.

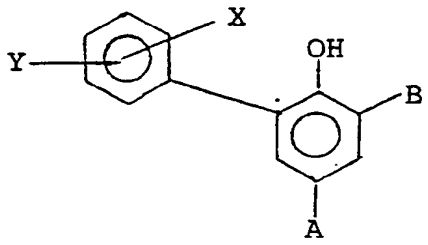
The compounds of formula X are prepared by treating



XI

with nitrous acid or sodium nitrite in acid. The compounds of formula XI are known or easily prepared according to methods in the literature.

The foregoing intermediates of the formula



XII

and salts thereof, wherein A is NH_2 or lower alkyl-$\overset{O}{\overset{\|}{C}}$-NH, B is hydrogen or $CH_2NR_1R_2$ and X, Y, R_1 and R_2 are as previously defined with the proviso that when A is NH_2; B is $CH_2NR_1R_2$ are new compounds and part of the invention.

The compounds of formula I form salts with any of a variety of organic or inorganic acids. The preferred acids are those acids which would give rise to pharmaceutically acceptable salts, such as acetic, citric, lactic, tartaric, hydrochloric, sulfuric, phosphoric, etc. In addition, certain of the compounds of formula I form salts with any of a variety of bases. The preferred bases are those bases which would give

rise to pharmaceutically acceptable salts, such as sodium hydroxide, potassium hydroxide, calcium hydroxide, etc.

Certain of the compounds of the invention may exist in the form of hydrates or solvates. These forms are considered to be equivalent to the compounds of the invention and encompassed by formula I and its salts.

The compounds of the invention are new chemical compounds that are useful as pharmacological agents. The compounds are potent antimalarial agents. The compounds exhibit the highly desirable property of not only exhibiting a marked activity against normal malarial parasite strains, but also against resistant strains.

The compounds of the invention may be administered orally or parenterally. Surprisingly, the compounds of the invention are also excellent repository antimalarials. It does not appear to be necessary to have a typical repository salt, such as the pamoate salt, to achieve a repository effect, although the effect may be enhanced by the use of such a salt.

When administered orally or parenterally, the dose is adjusted to the condition of the individual patient; however, the usual mammalian daily dose range is from about 0.1 mg/kg of body weight to about 25 mg/kg of body weight, preferably 0.5 mg/kg to 5.0 mg/kg. Thus, a 70 kg mammal would have administered about 7.0 mg to about 1.8 g over a twenty-four hour period.

The above employed pharmaceutical compositions are produced by formulating a compound of the foregoing formula (as an active ingredient) in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, lozenges, and pills; as well as powders and aqueous and non-aqueous oral solutions and suspensions and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being

subdivided into individual doses by such means as measurement into a teaspoon or other standard container. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol; glycerine, sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

The percentage of the active ingredient in the foregoing compositions can be varied within wide limits but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primarily liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present. The compositions of the invention preferably contain from 1 to 1,000 mg of the active ingredient per dosage unit so that the entire amount to be administered during a day can be made up from a reasonable number of dosage units.

Compounds of the invention were tested against a normal drug-sensitive strain of Plasmodium berghei in mice by the parenteral route by a procedure described in J. Med. Chem., 1043 (1967). The compounds were

dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose seventy-two hours post infection. Extension of the mean survival time of the treated mice is interpreted as evidence of anti-malarial activity. Compounds are arbitrarily considered to be "active" when they produce at least a 100 percent increase in the mean survival time of treated mice. Animals that survive to sixty days are considered "cured" (termed "C" in Tables I and II). The mean survival time (MST) of infected control mice ranges from 6.1-6.3 days while the numbers in parentheses in Tables I and II indicate extension of survival time over the controls as an average for those animals of the five animal group not "cured". Table I compares a preferred compound of the invention to the widely used antimalarial, amodiaquine while Table II shows the high degree of activity of a large number of compounds of the invention.

Studies were also conducted with infections resulting from inoculations of owl monkeys with trophozoites of the chloroquine-pyrimethamine-resistant Vietnam Smith strain of P. Falciparum; the chloroquine-quinine-resistant, pyrimethamine-susceptible Vietnam Oak Knoll strain of P. Falciparum; or the pyrimethamine-resistant Uganda Palo Alto strain of P. Falciparum. The test method is described in L. H. Schmidt, Trans. R. Soc. Trop. Med. Hyg. 67 446 (1973).

The test showed that 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-[1,1'-biphenyl]-2-ol, 1-oxide and 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl]-[1,1'-biphenyl]-2-ol-1-oxide were curative against the Vietnam Smith and Vietnam Oak Knoll strains when administered orally at 2.0 mg/kg/day for a three day period and 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-[1,1'-biphenyl]-2-ol and 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-

dimethylethyl)amino]methyl]-2-[1,1'-diphenyl]-2-ol cleared the parasitemia of the Vietnam Smith, Vietnam Oak Knoll and Uganda Palo Alto strains when administered orally at 1.0 mg/kg/day for three days.

By the above method, it appears that 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-[1,1'-biphenyl]-2-ol-1-oxide and 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)-amino]methyl]-[1,1'-biphenyl]-2-ol-1-oxide have twenty times the activity of amodiaquine as curative agents against Oak Knoll strains of the malaria parasite and that 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol and 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl]-[1,1'-biphenyl]-2-ol have twenty times the activity of amodiaquine in clearing parasites in the above noted strain.

TABLE I

COMPARISON OF AMODIAQUINE* (A) AND 4'-CHLORO-5-[(7-CHLORO-4-QUINOLINYL)-AMINO]-3-[(DIETHYLAMINO)METHYL]-[1,1'-BIPHENYL]-2-OL (B) AGAINST TROPHOZOITE-INDUCED PLASMODIUM BERGHEI IN MICE

	MST after single s.c. dose						
	640	320	160	80	40	20	10
A	5C	5C	5C	2C	11.9	8.3	5.7
B	5C	5C	5C	5C	4C	3C	2C (14.2)

* Tested in the form of its dihydrochloride.

TABLE II

EFFECTS OF 5-[(7-CHLORO-4-QUINOLINYL)AMINO]-3-[(ALKYLAMINO)METHYL]-[1,1'-BIPHENYL]-2-OLS AND N -OXIDES AGAINST TROPHOZOITE-INDUCED P. BERGHEI IN MICE

				MST after single s.c. dose, mg/kg							
X	Y	NR_1R_2	Z	640	320	160	80	40	20	10	5
4-Cl	H	$N(Et)_2$	0	1C(11.9)	2C(11.2)	4C(11.9)	5C	5C	1C(33.7)	1C(30.2)	20.7
4-Cl	H	$N(Et)_2$	1	5C	5C	5C	5C	4C(37.9)	3C(20.9)	2C(14.2)	
4-Cl	H	$NHC(CH_3)_3$	0	16.7	1C(16.4)	2C(15.2)	3C(14.9)	4C(19.9)	3C(14.4)	2C(14.9)	1C(11.4)
4-Cl	H	$NHC(CH_3)_3$	1	4C(13.9)	4C(13.9)	3C(13.4)	2C(20.6)	4C(24.9)	4C(28.9)	1C(26.3)	1C(10.3)
3-Cl	H	$N(Et)_2$	0	4C(21.9)	5C	4C(31.9)	2C(31.9)	2C(25.2)	15.7	15.5	3.9
3-Cl	H	$N(Et)_2$	1	3C(16.4)	4C(21.9)	5C	2C(25.6)	1C(25.9)	16.5	9.7	2.1
3-CF_3	H	$N(Et)_2$	0	4C(29.0)	3C(21.9)	4C(21.9)	2C(28.2)	3C(37.5)	13.1	1C(15.2)	13.5
3-CF_3	H	$N(Et)_2$	1	4C(27.9)	1C(24.9)	21.1	11.7	8.1	6.9		
2-Cl	H	$N(Et)_2$	0	5C	4C(41.9)	4C(41.9)	5C	3C(40.9)	2C(17.2)		
2-Cl	H	$N(Et)_2$	1	5C	2C(37.9)	2C(18.9)	2C(14.9)	9.4	6.2	2.6	6.4

(continued)

X	Y	NR_1R_2	Z	640	320	160	80	40	20	10	5
2-OMe	H	$N(Et)_2$	0	5C	2C(37.9)	2C(18.9)	2C(14.9)	10.3	8.9		
2-OMe	H	$N(Et)_2$	1	3C(37.4)	1C(36.2)	2C(8.9)	8.7	6.9	0.7		
3-Cl	4-Cl	H	$N(Et)_2$	0	3C(10.9)	5C	5C	4C(33.4)	2C(28.9)	15.7	0.9	0.3
3-Cl	4-Cl	H	$N(Et)_2$	1	5C	5C	2C(29.1)	2C(25.7)	1C(21.2)	10.5	5.9	0.7
3-Cl	4-Cl	H		0	3C(33.9)	3C(25.9)	4C(27.4)	1C(30.2)	20.0	8.3	0.1	-0.1
3-Cl	4-Cl	H		1	5C	3C(24.4)	2C(25.4)	8.8	7.9	2.3	0.7	
3-Cl	4-Cl	H	$NHC(CH_3)_3$	0	4C(16.4)	3C(14.4)	4C(13.4)	4C(30.4)	3C(27.4)	1C(10.5)	9.7	6.1
3-Cl	4-Cl	H	$NHC(CH_3)_3$	1	5C	3C(25.9)	1C(25.9)	1C(23.2)	12.0	5.9	2.9	0.5
$4-OCH_3$		H	$N(Et)_2$	0	5C	3C(28.9)	2C(16.1)	1C(12.4)	10.0	4.3	2.9	0.1
$4-OCH_3$		H	$N(Et)_2$	1	4C(27.4)		7.3		3.5	3.7	1.1	0.1
4-Cl		H	$NHCHC_2H_5$ | CH_3	0	5C(14.2)	1C(12.5)	3C(11.9)	3C(14.0)	4C(15.0)	3C(21.0)	23.6	11.0

(continued)

X	Y	NR_1R_2	Z	640	320	160	80	40	20	10	5
4-Cl	H	$NHCHC_2H_5$ | CH_3	1	3C(11.6)	3C(17.1)	4C(14.6)	3C(23.6)	3C(24.3)	2C(13.8)	7.2	
4-Cl	H	$NHCH_2CH(CH_3)_2$	0	3C(14.1)	2C(11.3)	4C(7.6)	5C	4C(37.6)	2C(19.6)	14.8	5.2
4-CF_3	H	$N(Et)_2$	0	12.1		1C(12.2)		2C(17.5)			
4-CF_3	H	$NHC(CH_3)_3$	0	13.7		1C(14.5)		2C(16.8)			
4-CF_3	H	$N(C_2H_5)_2$	1	1C(12.3)		2C(20.5)		2C(25.2)			
4-Cl	H	$N(C_3H_7)_2$	0	3C(13.3)	4C	2C(26.6)	3C(27.6)	1C(22.2)	12.4	6.8	
4-Cl	H	$N(CH_3)_2$	0	1C(18.7)	1C(14.4)	5C	4C(45.4)	1C(29.7)	1C(24.7)	20.4	(14.2)
4-Cl	H	$N(CH_3)_2$	1	1C(20.7)	3C(17.9)	5C	3C(21.9)	3C(21.4)	2C(19.7)	1C(17.8)	17.6
4-Cl	H	$N(C_4H_9)_2$	0	3C(34.4)	24.0	17.0	12.6	8.2	4.6		
4-Cl	H	$N(C_4H_9)_2$	1	1C(31.7)	21.2	12.2	8.0	2.2			
4-F	H	$N(Et)_2$	0	14.8		12.8		2C(13.4)			
4-OH	H	$N(Et)_2$	0	1C(4.1)	2C(3.6)	6.8	4.8				
4-F	H	$N(Et)_2$	1	15.0	4C(8.6)	5C	4C(23.6)	2C(23.6)	21.4		
4-F	H	$NHC(CH_3)_3$	0	14.4	16.6	1C(11.9)	1C(12.4)	4C(10.6)	4C(17.6)		
4-Cl	H	NHC_6H_{11}	0	4C(17.6)	4C	4C(20.6)	3C(23.6)	1C(21.4)	1C(13.1)		

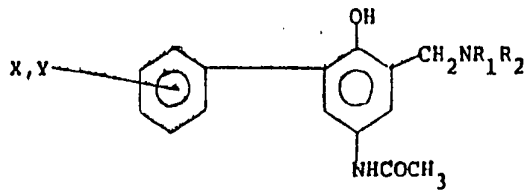
STARTING MATERIALS

A. 5-Amino-4'-chloro-3-[(diethylamino)methyl]-1,1'-biphenyl-2-ol,dihydrochloride may be prepared as follows:

A solution of 6.5 g of N-[4'-chloro-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide, 2.0 ml of 37% aqueous formaldehyde and 2.6 ml of diethylamine in 20 ml of ethanol is heated under reflux for 7 hr. After the second, fourth and sixth hours, additional portions of one ml of formaldehyde and one ml of diethylamine are added. The mixture is allowed to remain overnight, the solvent is removed in vacuo, and the residue is dissolved in ether. The solution is washed with water and with saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness in vacuo. The residue is dissolved in ethyl acetate and chromatographed over 200 g of alumina (Alcoa F-20) with ethyl acetate to provide N-[4'-chloro-5-[(diethylamino)-methyl]-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide. A mixture of this material (8.3 g) in 15 ml of water and 17 ml of concentrated hydrochloric acid is heated under reflux for 2 hr, allowed to cool overnight, and evaporated in vacuo to provide 5-amino-4'-chloro-3-[(diethylamino)methyl]-1,1'-biphenyl-2-ol,dihydrochloride. (Table III, compound a.)

Additional starting materials, which may be prepared by the above route, are shown in Table III.

TABLE III



No.	X	Y	NR_1R_2	mp°C	Recrystallization Solvent
a)	4-Cl	H	$N(C_2H_5)_2$	--	---
b)	4-Cl	H	$NHC(CH_3)_3$ (H_3PO_4)	241-3(dec)	---
c)	4-Cl	H	$NHCHC_2H_5$ CH_3	oil	---
d)	4-Cl	H	$NHCH_2CH(CH_3)_2$	gum	---
e)	4-Cl	H	$N(C_3H_7)_2$	oil	---
f)	4-Cl	H	$N(CH_3)_2$	glass	---
g)	4-Cl	H	$N(C_4H_9)_2$	oil	---
h)	4-Cl	H	$NH(C_6H_{11})$		
i)	3-Cl	H	$N(C_2H_5)_2$	oil	Chromatography
j)	3-CF_3	H	$N(C_2H_5)_2$	115-8	$CH_3CHOHCH_3$-H_2O
k)	2-Cl	H	$N(C_2H_5)_2$	gum	Chromatography

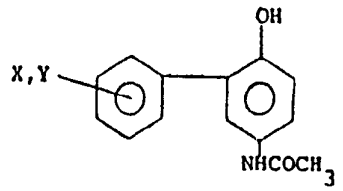
No.	X	Y	NR_1R_2	mp°C
l)	4-Cl	3-Cl	$N(C_2H_5)_2$	75-85
m)	4-Cl	3-Cl	$N(CH_2)_4$	gum
n)	4-Cl	3-Cl	$NHC(CH_3)_3$	164-5
o)	4-CF_3	H	$N(C_2H_5)_2$	glass
p)	4-CF_3	H	$NHC(CH_3)_3$	oil
q)	4-F	H	$N(C_2H_5)_2$	oil
r)	4-OH	H	$N(C_2H_5)_2$	oil
s)	2-CF_3	H	$N(C_2H_5)_2$	glass
t)	3-F	H	$N(C_2H_5)_2$	oil
u)	4-CH_3S	H	$N(C_2H_5)_2$	oil
v)	2-F	H	$N(C_2H_5)_2$	oil
w)	4-F	H	$NHC(CH_3)_3$	oil

B. N-[4'-Chloro-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide.

A solution of 7.0 g of 5-amino-4'-chloro-[1,1'-biphenyl]-2-ol and 3 ml of acetic anhydride in 400 ml of toluene is treated with charcoal, heated to boiling, filtered and cooled. The solid is recrystallized from toluene to give N-[4'-chloro-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide, mp 135°C. (Table IV, compound a.)

Additional starting materials, which may be prepared by the above route, are shown in Table IV.

TABLE IV



No.	X	Y	mp°C	Recrystallization Solvent
a)	4-Cl	H	135	Toluene
b)	3-Cl	H	152-4	Toluene[1]
c)	3-CF_3	H	145-7	Toluene
d)	2-Cl	H	111-7	Toluene[1]
e)	4-Cl	3-Cl	187-9	Toluene[1]
f)	4-CF_3	H	186-8	Toluene-$CH_3CHOHCH_3$
g)	4-F	H	glass	---
h)	4-CH_3O-$(CH_2)_2OCH_2O$	H H	glass	---
i)	2-CF_3	H	gum	---
j)	3-F	H	---	---
k)	4-CH_3S	H	145-7	CH_3CN
l)	2-F	H	---	---

1) Triturated with the solvent.

C. 5-Amino-4'-chloro-[1,1'-biphenyl]-2-ol.

A mixture of 99.5 g of 2-iodoanisole, 202 g of 1-chloro-4-iodobenzene and 400 g of copper powder is stirred in an oil bath at 220-240° for 6 hr, allowed to cool overnight, and extracted with chloroform. The extract is dried over anhydrous sodium sulfate and concentrated to dryness in vacuo. The residue is taken up in 1 liter of hot pentane, filtered, and applied on a column of 800 g of silica gel equilibrated with hexane. Elution with hexane containing 2% ethyl ether provided 4'-chloro-2-methoxy-1,1'-biphenyl; mp 50-52°C after recrystallization from hexane.

A mixture of 31.5 g of 4'-chloro-2-methoxy-1,1'-biphenyl and 126 ml of 48% hydrobromic acid in 600 ml of glacial acetic acid is heated under reflux for 18 hr, allowed to cool, poured into 1 liter of water and extracted with ether. The extract is washed with water, dried over sodium sulfate and concentrated. The residue is recrystallized from hexane to give 4'-chloro-[1,1'-biphenyl]-2-ol, mp 49.5-52°C.

A solution of 4 g of 4'-chloro-[1,1'-biphenyl]-2-ol in 63 ml of glacial acetic acid and 40 ml of water is chilled to 5°C and treated dropwise with a solution of 1.5 g of sodium nitrite in 7 ml of water. The mixture is stirred several hours at 5°C and filtered. Recrystallization first from 33% acetic acid and then from toluene gives 2-(4-chlorophenyl)-2,5-cyclohexadiene-1,4-dione,4-oxime, mp 182-184°C (dec).

To a stirred suspension of 7.8 g of 2-(4-chlorophenyl)-2,5-cyclohexadiene-1,4-dione,4-oxime in 170 ml of 1N sodium carbonate is added in portions 23 g of sodium dithionite. The mixture is stirred for 5 hrs, filtered, washed with water and recrystallized from toluene to give 5-amino-4'-chloro-[1,1'-biphenyl]-2-ol, mp 189-191°C.

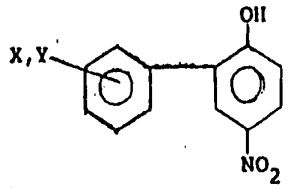
D. N-[2'-Chloro-6-hydroxy[1,1'-biphenyl]-3-yl]-acetamide.

A solution of 19.9 g of 2'-chloro-5-nitro[1,1'-biphenyl]-2-ol in 200 ml of methanol is hydrogenated over 0.7 g of Raney nickel at an initial pressure of 52 psi at room temperature for 23 hrs. An additional gram of catalyst is added and hydrogenation continued for another 8 hrs. The mixture is filtered into 8.2 ml of acetic anhydride, warmed on the steam bath for 20 minutes and concentrated to dryness in vacuo. Chromatography of the residue over 190 g of silica gel with ethyl acetate affords a gum which is triturated with toluene to give N-[2'-chloro-6-hydroxy[1,1'-biphenyl]-3-yl]acetamide, mp 111-117°C.

A mixture of 18.9 g of sodium nitromalonaldehyde in 210 ml of water and 76 ml of 10% sodium hydroxide is combined with a solution of 25 g of o-chlorophenyl-acetone in 265 ml of ethanol. The mixture is allowed to remain at room temperature for 20 hrs, concentrated in vacuo to remove the ethanol, extracted with ether, and the aqueous layer is acidified with 10N hydrochloric acid. The resulting oil is extracted with ether. The extract is washed, dried and concentrated in vacuo to dryness. Recrystallization from toluene gives 2'-chloro-5-nitro-[1,1'-biphenyl]-2-ol, mp 155-157°C.

Additional starting materials, which may be prepared by the same route are shown in Table V.

TABLE V



No.	X	Y	mp°C	Recrystallization Solvent
a)	3-Cl	H	180-2	Toluene CH_3CH_2OH
b)	3-CF_3	H	185-7	Toluene $CH_3CHOHCH_3$
c)	4-Cl	3-Cl	243-5	$CH_3CHOHCH_3$
d)	4-CF_3	H	185-8	Toluene
e)	4-F	H	182-4(dec)	Ether-hexane
f)	2-CF_3	H	125-7	CH_2Cl_2-hexane
g)	3-F	H	143-6	Toluene
h)	4-CH_3S	H	162-5	Toluene
i)	2-F	H	---	---

EXAMPLE 1

4'-chloro-5-[(7-chloro-4-quinolinyl)amino-3-[(diethylamino)methyl]-[1,1'-biphenyl]-2-ol,1-oxide.

A mixture of N-[4'-chloro-5-[(diethylamino)-methyl]-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide (8.3 g) in 15 ml of water and 17 ml of concentrated hydrochloric acid is heated under reflux for 2 hrs, allowed to cool overnight, and evaporated in vacuo to provide 5-amino-4'-chloro-3-[(diethylamino)methyl]-1,1'-biphenyl-2-ol,dihydrochloride.

A mixture of 3.3 g of 4,7-dichloroquinoline,1-oxide and 5.7 g of 5-amino-4'-chloro-3-[(diethylamino)-methyl]-1,1'-biphenyl-2-ol,dihydrochloride in 130 ml of ethanol is heated under reflux for 1.5 hrs, cooled and concentrated to dryness in vacuo. The dark residue is taken up in a mixture of 10% sodium carbonate and chloroform, and the resulting gold precipitate is collected and washed with 2-propanol to afford 4.5 g of crude product. Chromatography on silica with 10% methanol in ethyl acetate followed by recrystallization from ethanol provides 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-[1,1'-biphenyl]-2-ol,1-oxide, mp 210-213°C (dec).

EXAMPLE 2

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol.

A mixture of 8.3 g of N-[4'-chloro-5-[(diethyl-amino)methyl]-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide in 15 ml of water and 17 ml of concentrated hydrochloric acid is heated under reflux for 2 hrs, allowed to cool overnight, and evaporated in vacuo. The residue and 4.8 g of 4,7-dichloroquinoline in 40 ml of ethanol is heated under reflux for 1.5 hrs, allowed to cool and poured with stirring into 700 ml of 2N ammonium hydroxide. The precipitate is collected, washed with water and dissolved in chloroform. The

extract is washed with dilute sodium hydroxide and with water, dried over anhydrous potassium carbonate, filtered and evaporated in vacuo. The residue is recrystallized from an acetonitrile-toluene mixture (800 ml:300 ml) to provide 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol, mp 229-232°C.

EXAMPLE 3

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl][1,1'-biphenyl]-2-ol.

A mixture of 1.8 g of N-[4'-chloro-5-[[(1,1-dimethylethyl)amino]methyl]-6-hydroxy[1,1'-biphenyl]-3-yl]acetamide and 12 ml of 6N-hydrochloric acid is heated under reflux for 1.5 hrs and concentrated to dryness in vacuo to afford 5-amino-4'-chloro-3-[[(1,1-dimethylethyl)amino]methyl][1,1'-biphenyl]-2-ol which is combined with 1 g of 4,7-dichloro-quinoline and 15 ml of ethanol. The mixture is heated under reflux for 1 hr, allowed to cool, and poured into 250 ml of water containing 10 ml of concentrated ammonium hydroxide. The resulting precipitate is collected and dissolved in chloroform; the solution is washed with 1% sodium hydroxide solution and with water, dried over sodium sulfate, and evaporated in vacuo to dryness. Recrystallization from acetonitrile gives 4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl][1,1'-biphenyl]-2-ol, mp 228°C (dec).

EXAMPLE 4

2'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol.

A mixture of 2.5 g of N-[2'-chloro-5-[(diethylamino)methyl]-6-hydroxy-[1,1'-biphenyl]-3-yl]acetamide (solvated with 0.2 mole of ethyl acetate) in 15 ml of 6N hydrochloric acid is heated under reflux for 1 hr,

diluted with ethanol, concentrated in vacuo, combined with additional ethanol and concentrated again. A mixture of the residue and 1.4 g of 4,7-dichloroquinoline in 50 ml of ethanol is heated under reflux for 2 hrs, allowed to cool, and made basic with ammonium hydroxide. The precipitate is collected and dissolved in a mixture of dichloromethane and 5% aqueous ammonium hydroxide. The organic layer is washed with water, dried and concentrated to dryness in vacuo. Recrystallization from toluene provides 2'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl][1,1'-biphenyl]-2-ol, mp 231-234°C (dec).

TABLE VI

Physical Data for 5-[(7-Chloro-4-quinolinyl)amino]-3-[(alkylamino)methyl][1,1'-biphenyl]-2-ols and N -oxides[1]

X	Y	NR_1R_2	Z	mp°C	Recrystallization Solvent
4-Cl	H	$N(Et)_2$	0	229-232	MeOH-Toluene
4-Cl	H	$N(Et)_2$	1	210-213	EtOH
4-Cl	H	$NHC(CH_3)_3$	0	228(dec)	MeCN
4-Cl	H	$NHC(CH_3)_3$	1	196(dec)	MeCN
3-Cl	H	$N(Et)_2$	0	238-240(dec)	2-Butanone
3-Cl	H	$N(Et)_2$	1	224-225(dec)	MeOH
3-CF_3	H	$N(Et)_2$	0	234-236(dec)	EtOH
3-CF_3	H	$N(Et)_2$	1	227-229(dec)	MeOH
2-Cl	H	$N(Et)_2$	0	231-234(dec)	Toluene
2-Cl	H	$N(Et)_2$	1	223-225(dec)	2-PrOH(trit.)

(continued)

X	Y	NR_1R_2	Z	mp°C	Recrystallization Solvent
$2-OCH_3$	H	$N(Et)_2$	0	130-133 (196-198)	2-PrOH-H_2O
$2-OCH_3$	H	$N(Et)_2$	1	220-222(dec)	2-PrOH(trit.)
3-Cl	4-Cl	$N(Et)_2$	0	242-244(dec)	2-PrOH-Toluene
3-Cl	4-Cl	$N(Et)_2$	1	186-190(dec)	2-PrOH(trit.)
3-Cl	4-Cl	$N(CH_2)_4$	0	287-288(dec)	EtOH
3-Cl	4-Cl	$N(CH_2)_4$	1	245-246(dec)	DMF
3-Cl	4-Cl	$NHC(CH_3)_3$	0	220-222(dec)	Toluene
3-Cl	4-Cl	$NHC(CH_3)_3$	1	200-202(dec)	EtAc-CH_2Cl_2
$4-OCH_3$	H	$N(Et)_2$	0	206-209	MeCN
$4-OCH_3$	H	$N(Et)_2$	1	200-201(dec)	MeCN-2-PrOH
4-Cl	H	$NHCHC_2H_5$ | CH_3	0	285-287(dec)	EtOH
4-Cl	H	$NHCHC_2H_5$ | CH_3	1	193-195(dec)	MeCN-2-PrOH
4-Cl	H	$NHCH_2CH(CH_3)_2$	0(·2HCl)	277-280(dec)	EtOH

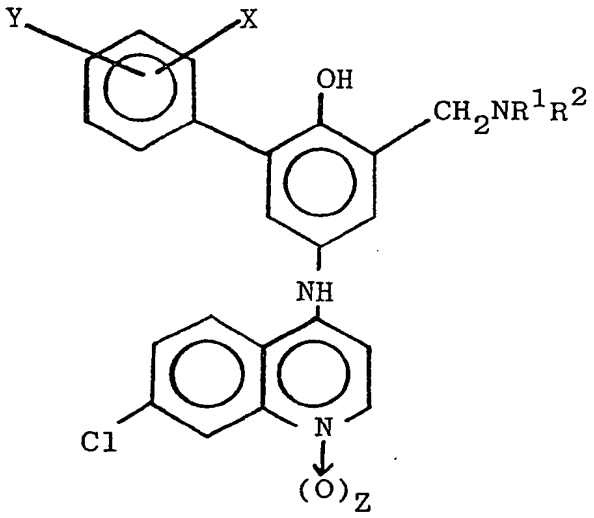
(continued)

X	Y	NR_1R_2	Z	mp°C	Recrystallization Solvent
4-CF_3	H	$N(Et)_2$	0	227-229(dec)	MeCN
4-CF_3	H	$NHC(CH_3)_3$	0(·2HCl)	292-294(dec)	EtOH
4-CF_3	H	$N(C_2H_5)_2$	1	169-172(dec)	----
4-Cl	H	$N(C_3H_7)_2$	0	220-222	DMF-MeOH
4-Cl	H	$N(CH_3)_2$	0	222-226	EtOH
4-Cl	H	$N(CH_3)_2$	1	160-175	2-PrOH
4-Cl	H	$N(C_4H_9)_2$	0	166-170	Cyclohexane
4-Cl	H	$N(C_4H_9)_2$	1	160-166	CH_3CN
4-F	H	$N(Et)_2$	0	225-228(dec)	EtOH
4-OH	H	$N(Et)_2$	0	240-245(dec)	EtOH-H_2O
4-F	H	$N(Et)_2$	1	151-154(dec)	$CHCl_3$-EtAc
4-F	H	$NHC(CH_3)_3$	0	dec >154	EtOH-H_2O
4-Cl	H	NHC_6H_{11}	0	106-120(dec)	Cyclohexane

1) Compounds wherein Z is 1 are prepared by the process of Example 1 and compounds wherein Z is 0 are prepared by the process of Example 2.

CLAIMS (for all States other than Austria):

1. A compound having the following general formula:



or a pharmaceutically acceptable salt thereof; wherein X is a hydrogen, fluorine, bromine or chlorine atom or a lower alkyl radical; Y is a chlorine, fluorine or bromine atom or a trifluoromethyl, lower alkoxy, cyano, hydroxy, nitro, lower alkylthio, amino, lower alkyl amino, di(lower alkyl) amino, pyrrolidino or piperidino radical; R^1 and R^2, which are the same or different, are each a hydrogen atom or a lower alkyl radical, or R^1R^2N taken together is a pyrrolidino, piperidino or homopiperidino radical of which the heterocyclic ring is unsubstituted or substituted by from one to four lower alkyl radicals; Z is zero or one; a lower alkyl radical is an alkyl radical containing from one to six carbon atoms; and a lower alkoxy radical is an alkoxy radical containing from one to six carbon atoms.

2. A compound according to claim 1, wherein X is a hydrogen or chlorine atom, Y is a chlorine or fluorine atom, R^1 is a lower alkyl radical, R^2 is a hydrogen atom or a lower alkyl radical, and Z is zero or one.

3. A compound according to claim 1 or 2, wherein X is in the 3-position and Y is in the 2- or 4-position.

4. A compound according to claim 1, having one of the following names;

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl] [1,1'-biphenyl]-2-ol,1-oxide;

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]- [1,1'-biphenyl]-2-ol;

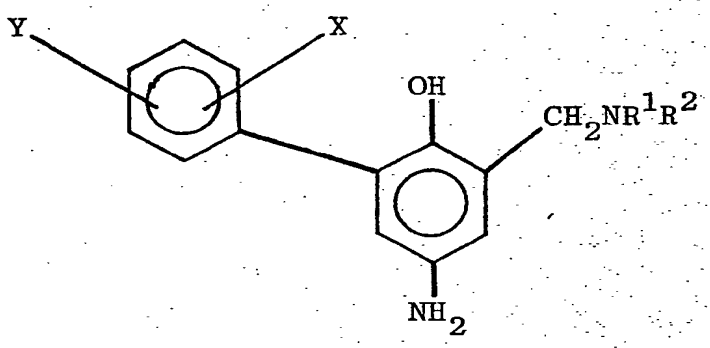
4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl] [1,1'-biphenyl]-2-ol;

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl]-[1,1'-biphenyl]-2-ol,1-oxide;

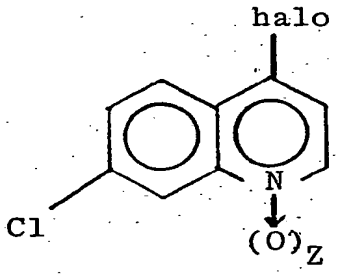
2'-choro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl] [1,1'biphenyl]-2-ol; and

3',4'-dichloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl] [1,1'-biphenyl]-2-ol; or a salt thereof.

5. A process for producing a compound according to claim 1, which comprises coupling a compound having the following general formula:-



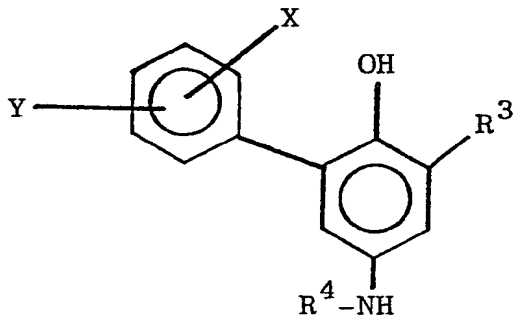
with a compound having the following general formula:-



wherein R^1, R^2, X, Y and Z are as defined in Claim 1 and halo is chloro, bromo or iodo.

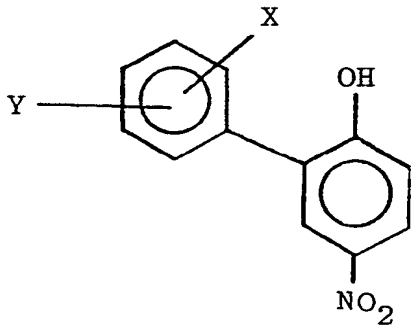
6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, and a pharmaceutical carrier therefor.

7. A compound having the following general formula:-



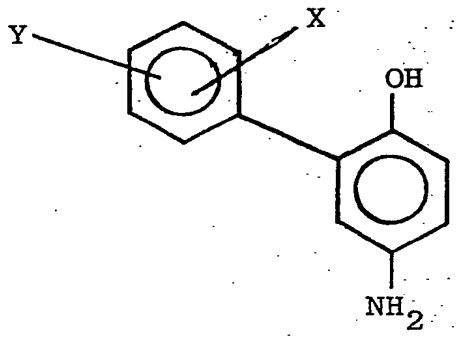
where R^3 is $-CH_2NR^1R^2$ or a hydrogen atom, R^4 is a lower alkyl carbonyl radical or a hydrogen atom, and X, Y, R^1 and R^2 are as defined in claim 1, with the proviso that, when R^4 is a hydrogen atom, R^3 is $-CH_2NR^1R^2$.

8. A process for producing a compound having the formula shown in claim 7 but in which R^3 and R^4 are each hydrogen atoms, and in which X and Y are as defined in claim 1, which comprises reducing a compound having the following general formula:-



wherein X and Y are as defined in Claim 1.

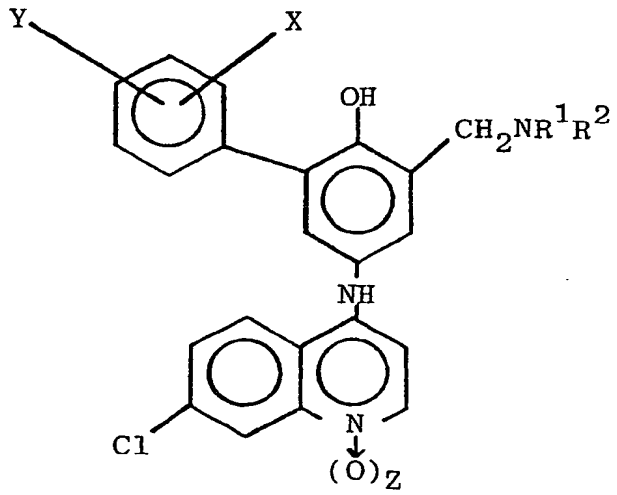
9. A process for producing a compound having the formula shown in claim 7 wherein R^3 is a hydrogen atom and R^4 is a lower alkyl carbonyl radical, and X and Y are as defined in claim 1, which process comprises acylating a compound having the following general formula:-



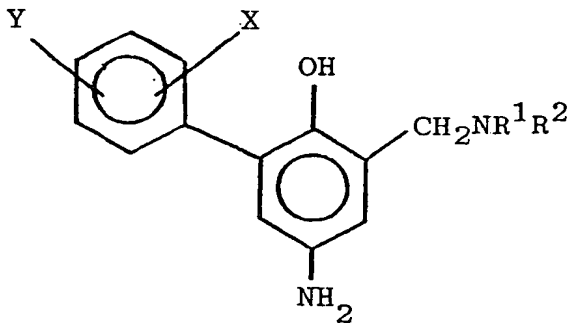
wherein X and Y are as defined in claim 1.

CLAIMS for Austria alone:

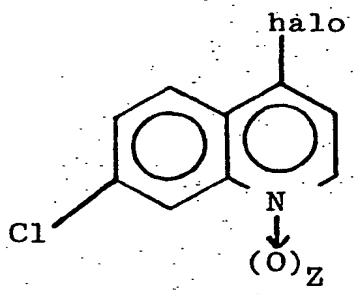
1. A process for producing a compound having the following general formula:-



or a pharmaceutically acceptable salt thereof; wherein X is a hydrogen, fluorine, bromine or chlorine atom or a lower alkyl radical; Y is a chlorine, fluorine or bromine atom or a trifluoromethyl, lower alkoxy, cyano, hydroxy, nitro, lower alkylthio, amino, lower alkyl amino, di(lower alkyl) amino, pyrrolidino or piperidino radical; R^1 and R^2, which are the same or different, are each a hydrogen atom or a lower alkyl radical, or R^1R^2N taken together is a pyrrolidino, piperidino or homopiperidino radical of which the heterocyclic ring is unsubstituted or substituted by from one to four lower alkyl radicals; Z is zero or one; a lower alkyl radical is an alkyl radical containing from one to six carbon atoms; and a lower alkoxy radical is an alkoxy radical radical containing from one to six carbon atoms: the process comprises coupling a compound having the following general formula:-



with a compound having the following general formula:-



wherein R^1, R^2, X, Y and Z are as defined above and halo is chloro, bromo or iodo: and, where necessary, converting the produced compound to the desired salt.

2. A process according to claim 1, wherein X is a hydrogen or chlorine atom, Y is a chlorine or fluorine atom, R^1 is a lower alkyl radical, R^2 is a hydrogen atom or a lower alkyl radical, and Z is zero or one.

3. A process according to claim 1 or 2, wherein X is in the 3-position and Y is in the 2- or 4- position.

4. A process according to claim 1 wherein the compound produced is one of:-

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl] [1,1'-biphenyl]-2-ol,1-oxide;

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl]-[1,1'-biphenyl]-2-ol;

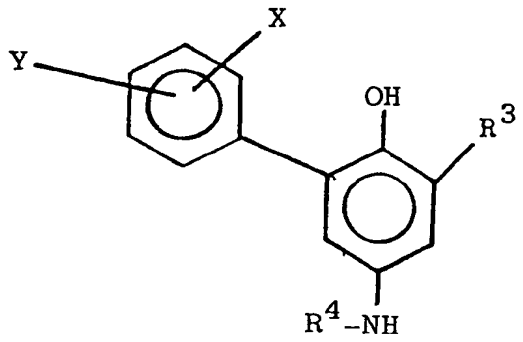
4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl] [1,1'-biphenyl]-2-ol;

4'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1-dimethylethyl)amino]methyl]-[1,1'-biphenyl]-2-ol,1-oxide;

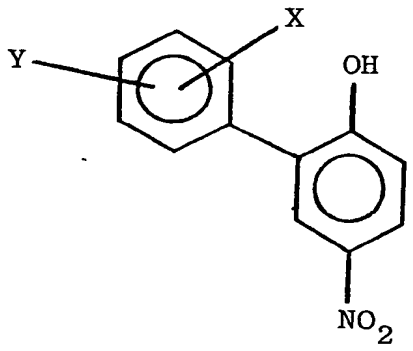
2'-chloro-5-[(7-chloro-4-quinolinyl)amino]-3-[(diethylamino)methyl] [1,1'-bipheynyl]-2-ol;

3',4'-dichloro-5-[(7-chloro-4-quinolinyl)amino]-3-[[(1,1dimethylethyl)amino]methyl] [1,1'-biphenyl]-2-ol, and salts thereof.

5. A process for producing a compound of the following general formula:-

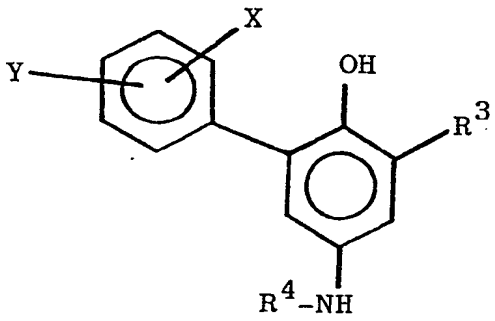


wherein R^3 and R^4 are each a hydrogen atom and X and Y are as defined in claim 1, which comprises reducing a compound of the following formula:

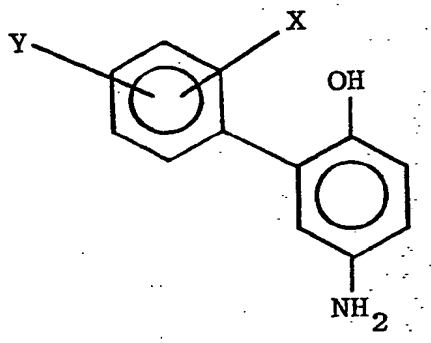


wherein X and Y are as defined in claim 1.

6. A process for producing a compound having the following general formula:-



wherein R^3 is a hydrogen atom, R^4 is a lower alkyl carbonyl radical, and X and Y are as defined in claim 1, which comprises acylating a compound of the following formula:-



wherein X and Y are as defined in claim 1.

7. A process according to any one of claims 1 to 4, wherein the hydroxy compound which is coupled is produced in accordance with the process of claim 5 or 6.

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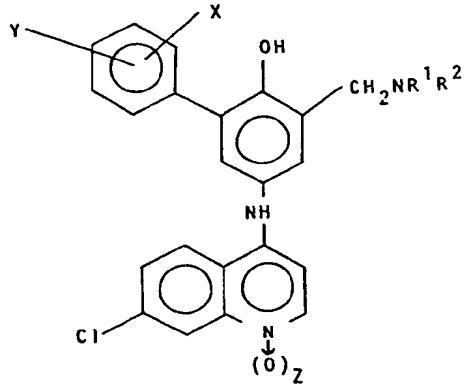
(54) **Substituted-5-((7-chloro-4-quinolinyl)amino)-3-(amino-methyl)-(1,1'-biphenyl)-2-ol compounds; processes for their production; pharmaceutical compositions containing the compounds; intermediate compounds for use in said processes; and production of the intermediates.**

(57) Substituted-5-[(7-chloro-4-quinolinyl)amino]-3-(amino-methyl)-[1,1'-biphenyl]-2-ol compounds and salts thereof; and processes for their production are disclosed. In addition, antimalarial pharmaceutical compositions including such compounds and methods of treatment employing the compositions are taught. Also disclosed are intermediates for use in producing the substituted compounds. The substituted compounds are those of the formula:-



wherein X is a hydrogen, fluorine, bromine or chlorine atom or a lower alkyl radical; Y is a chlorine, fluorine or bromine atom or a trifluoromethyl, lower alkoxy, cyano, hydroxy, nitro, lower alkylthio, amino, lower alkyl amino, di(lower alkyl) amino, pyrrolidino or piperidino radical; R^1 and R^2, which are the same or different, are each a hydrogen atom or a lower alkyl radical, or R^1R^2N taken together is a pyrrolidino, piperidino or homopiperidino radical of which the heterocyclic ring is unsubstituted or substituted by from one to four lower alkyl radicals; Z is zero or one.

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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
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	US - A - 2 474 823 (PARKE, DAVIS)	1,6
	GB - A - 974 348 (PARKE, DAVIS)	1,6
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CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 215/441
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C 07 C 91/44//
79/26

TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 215/441
215/60
A 61 K 31/47

CATEGORY OF CITED DOCUMENTS

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T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

Place of search	Date of completion of the search	Examiner
The Hague	20-01-1981	ALFARO

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